THE VAPOR PRESSURE OF ACETYLATED AMINO ACID ETHYL ESTERS[1]

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A semimicro ebulliometer was used in conjunction with a manostat and mercury Zimmerli gage to determine the vapor pressure–temperature curves of a number of acetylated amino acid ethyl esters over the pressure range of 2 to 90 mm. The amino acids whose derivatives have been studied are glycine, alanine, valine, leucine, isoleucine, phenylalanine, methionine, tyrosine, aspartic acid and pyrrolidonecarboxylic acid.

Although most of the acetylated amino acid ethyl esters have been prepared and distilled, the amount of information available on their boiling points and vapor pressures is very limited. Usually only the boiling points found during their preparation are available and these may be expressed as a range of temperature at a pressure known only to one significant figure. The best collection of such data has been reported by Cherbuliez and Plattner[3] who made boiling point readings at one or two pressures for eleven of the compounds.

More accurate vapor pressure data over a wider range of pressure were desired to study the possibilities of separating these compounds by distillation techniques. The vapor pressure–temperature curves over the range of 2 to 90 mm. pressure were, therefore, determined on purified materials using a regulated pressure system and a semimicro ebulliometer.

Experimental

The acetylated amino acid ethyl esters were prepared by various standard methods of acetylation and esterification of the amino acids and their derivatives. The nitrogen analysis[4] of each derivative agreed with the theoretical value.

Since the preparation of the N-acetylmethionine ethyl ester has not been described previously, the details of its synthesis are as follows: Methionine was esterified with alcoholic hydrogen chloride. The ester hydrochloride crystals were mixed with an equal weight of fused sodium acetate and double their weight of acetic anhydride, and heated on a steam-bath for one hour. The reaction mixture was extracted with chloroform. The extract was evaporated *in vacuo* and the residue was Claisen distilled at 1.3 mm. and 163–164°.

Anal. Calcd. for $C_9H_{17}O_3NS$: C, 49.3; H, 7.8; N, 6.4; S, 14.6. Found: C, 49.6; H, 7.6; N, 6.4; S, 14.8.

The vapor pressure measurements were made in the semimicro ebulliometer of Hoover, John and Mellon.[5] Pressure was regulated by means of a Ratchford and Fein mano-

stat[6] and measured with a mercury Zimmerli gage.[7] A series of determinations at increasing pressures was made for each compound. A 10–15 minute period of refluxing was used to assure stable pressure and temperature readings for each point. The thermometer was calibrated in the apparatus by determining the boiling points at atmospheric pressure of pure compounds which are accepted standards for thermometer calibration. The temperatures reported are, therefore, corrected temperatures.

Results

The numerous vapor pressure measurements obtained have been consolidated by calculating, according to the least squares method, the equations for the straight lines obtained by plotting the log of the vapor pressure against the reciprocal of the absolute temperature. The relationship of the lines for the various n-acetylated amino acid ethyl esters is shown in Fig. 1. The experimental points are shown on the alanine and methionine curves to give a visible representation of the closeness of the fit of the calculated line. The constants, A and B, for the equation of these lines, $\log P = A - B/T$, are given in Table I. The pressure is in mm. and the temperature, T, is in degrees Kelvin. The standard error of the estimate, $S_p = \sqrt{\Sigma d^2/n}$, is given in the third column of figures. From S_p

Table I

Constants for Vapor Pressure Equations for N$^\alpha$-Acetylamino Acid Ethyl Esters

Amino acid	A	B	S_p	70% limit, %	Points
Glycine	9.7488	3627	0.0090	2.4	11
DL-Alanine	9.3647	3408	.0140	3.5	9
DL-Valine	9.5313	3535	.0125	3.2	8
DL-Methionine	10.1663	4264	.0053	1.4	10
L-Leucine	10.1594	3906	.0092	2.4	16
L-Isoleucine	9.5376	3610	.0054	1.4	17
DL-Phenylalanine	10.1199	4306	.0023	0.8	6
L-Aspartic acid	9.7816	3970	.0139	3.8	6
L-Glutamic acid	8.9254	3509	.0087	2.5	6
DL-Pyrrolidone-2-carboxylic acid[a]	9.4941	3849	0106	2.7	9

[a] The pyrolidone-2-carboxylic acid was esterified but not acetylated.

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(2) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

(3) E. Cherbuliez and Pl. Plattner, *Helv. Chim. Acta*, **12**, 317 (1929).

(4) The authors are indebted to Dr. C. L. Ogg for the analysis of the compounds.

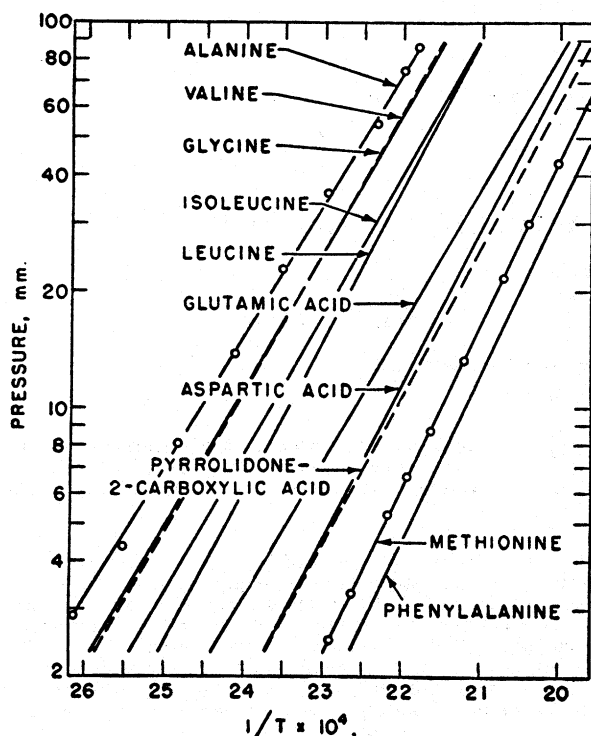(5) S. R. Hoover, H. John and E. F. Mellon, *Anal. Chem.*, in press.

(6) W. P. Ratchford and M. L. Fein, *ibid.*, **22**, 838 (1950).

(7) A. Zimmerli, *Ind. Eng. Chem., Anal. Ed.*, **10**, 283 (1938).

Fig. 1.—Vapor pressure–temperature relationsI{ips for the acetylated amino acid ethyl esters.

one can calculate the limits within which a certain percentage of the experimental points will agree with the values given by the curve. This limit calculated to include 70% of the experimental points is reported in column 4 as a percentage of the pressure value represented by the corresponding point on the curve. The average for this limit over all the data is about 2.5%. The number of observations on which each curve is based is given in column 5. The fewer number of points used for the aspartic and glutamic acid calculations was a reflection of their tendency to decompose slowly at elevated temperatures. An independent determination of six points on a second sample of the glutamic acid derivative gave the same curve as the original sample used.

A sample of N-acetyltyrosine ethyl ester melting at 80° was boiled in the micro-ebulliometer at 2.3 mm. and a temperature of 244.4°. There was no decomposition but only one point was obtained because the maximum temperature limit of the apparatus had been reached.

The data obtained from our experiments do not agree very closely with the corresponding points obtained by Cherbuliez and Plattner[3] but the differences are what might be expected between boiling points obtained during a Claisen distillation during preparation and the equilibrium boiling points of previously distilled material obtained in

an ebulliometer. The acetylated methionine ethyl ester reported on here also shows a difference in boiling point between the first purification distillation and the equilibrium value.

One of the more important observations was that of the lowered vapor pressure of the glycine derivative. Instead of being the most volatile of the derivatives because of its lower molecular weight and simplest structure, it has a vapor pressure which is very close to that of the valine derivative which is the third member of the homologous series; and considerably less than the vapor pressure of the alanine derivative which is the second member of the series.

A similar inversion phenomenon appears with the aspartic and glutamic acid derivatives. The lower molecular weight homolog—the aspartic acid derivative—actually has a lower vapor pressure than the higher homolog—the glutamic acid derivative. The pyrrolidonecarboxylic acid ethyl ester which can be formed by heating the acetylated diethyl glutamate also shows a vapor pressure which is lower than the glutamic acid derivative.

These differences are also reflected in the heats of vaporization which can easily be calculated as calories per mole by multiplying the slope constant "B" by the factor $2.3R = 4.577$. They can, therefore, probably be attributed to differences in the polar binding forces between the individual molecules with the molecules of the glycine and aspartic acid derivatives being held to each other more strongly than the molecules of the alanine and glutamic acid derivatives are held to each other. This effect of interaction between molecules is shown clearly with the leucine and isoleucine derivatives. These two compounds differ only in the location of a branching methyl group on the amino acid side chain. This methyl group on the beta carbon as in isoleucine, interferes with the polar activities of the amino group on the alpha carbon and gives this compound a lower heat of vaporization than when the methyl group is on the gamma carbon as in leucine.

The vapor pressure curves show that with only a few exceptions the vapor pressures of these acetylated amino acid ethyl esters are sufficiently different from each other to make possible their separation by distillation in an efficient fractionating column. The pressure best suited for a particular separation can also be predicted from the curves. One noteworthy separation—the separation of the leucine derivative from the isoleucine derivative—has been shown to occur very sharply at several millimeters pressure but no separation should be expected at 100 mm. pressure. This separation and the separation of other mixtures of these acetylated amino acid esters will be described in a subsequent publication.